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☐	L2	(GLP-1 | glucagon like peptide 1 or exendin$2) same ischemi$3 same (reperfus$4 and ((tissue|organ) adj (damage|death)))	6
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☐ 1. Document ID: US 20040002454 A1

L3: Entry 1 of 6 File: PGPB Jan 1, 2004

DOCUMENT-IDENTIFIER: US 20040002454 A1
TITLE: Treatment of acute coronary syndrome with GLP-1

Abstract Paragraph:
The invention relates to methods for treating a patient suffering from acute coronary syndrome, but who is not suffering from a Q-wave myocardial infarction, comprising administration of a therapeutically effective amount of a GLP-1 molecule. The GLP-1 can be self-administered, and can be administered in one or more doses, as needed, on an intermittent or continuous basis, to optimize metabolism in cardiac tissue and to prevent cardiac damage associated with ischemia.

Summary of Invention Paragraph:
[0012] (2) A method for treatment of a patient, comprising administering to the individual a therapeutically effective amount of a GLP-1 molecule, wherein the administration is after the onset of one or more of the following symptoms: chest pain lasting longer than 15 minutes, chest pain at rest, chest pain following minimal exertion, nausea, shortness of breath, palpitations, or dizziness. The above method, wherein the patient has not suffered a Q-wave MI prior to the onset of the symptom or symptoms. The above method, wherein the patient is suffering from unstable angina. The above method, wherein the patient is suffering from non-Q-wave cardiac necrosis. The above method, wherein the patient has a blood troponin I level of no more than 0.4 ng/ml. The above method, wherein the patient has a blood troponin T level of no more than 0.1 ng/ml. The above method, wherein the patient does not have elevated blood creatine kinase myocardial isoenzyme. The above method, wherein the patient does not have ST-segment elevation. The above method, wherein the patient does not exhibit a pathological Q-wave. The above method, wherein the administration occurs between the time of onset of the one or more symptoms, and the time the patient suffers a Q-wave MI. The above method, further comprising the step of continuing the administration of a GLP-1 molecule during the time that the patient suffers a Q-wave MI. The above method, further comprising the step of continuing the administration of a GLP-1 molecule after the time the patient suffers a Q-wave MI. The above method, wherein the patient has ischemic heart disease, or is at risk for developing ischemic heart disease. The above method, wherein the patient has one or more of the following cardiac abnormalities: congestive heart failure, worsening heart murmur due to mitral regurgitation, or evidence of cardiac conduction disturbances. The above method, wherein the patient has a normal ECG. The above method, wherein the patient has stable angina. The above method, wherein the patient administers the GLP-1 to himself. The above method, wherein the GLP-1 is administered in the form of a GLP-1-stick. The above method, wherein the GLP-1 is administered in a single dose. The above method, wherein the GLP-1 is administered in more than one dose. The above method, wherein the GLP-1 is administered continuously. The above method, wherein glucose, or a potassium salt, or a combination thereof, is co-administered with the GLP-1.

Summary of Invention Paragraph:
[0015] (5) A method for treatment of a patient with ischemic heart disease, or is at risk for developing ischemic heart disease, and who exhibits one or more of the following symptoms: nausea, shortness of breath, palpitations, or dizziness, and further wherein the patient does

not exhibit chest pain, comprising administering to the patient a therapeutically effective amount of a GLP-1 molecule, wherein the patient is not suffering a Q-wave MI. The above method, wherein the patient has a normal ECG.

Summary of Invention Paragraph:
[0018] Thus, the invention encompasses novel methods for the treatment of acute coronary syndrome, particularly unstable angina and non-Q-wave cardiac necrosis, with a GLP-1 molecule. The methods of the present invention can be used beginning at the earliest stages of ACS, prior to development of a Q-wave MI, to prevent damage associated with ischemia that occurs during Q-wave MI. The inventive therapeutic methods that use a GLP-1 molecule reverse or ameliorate the ischemia-induced damage that occurs during UA and NQCN. The methods of the invention further comprise continuing the treatment with a GLP-1 molecule during or after the time that a patient suffers from a QMI.

Summary of Invention Paragraph:
[0063] The timing and dosage of a GLP-1 molecule, according to the methods of the invention, will depend on the nature of the condition being treated. As discussed here, a GLP-1 molecule may be administered as soon as there is a symptom of cardiac distress, and the administration can be continued, either continuously or or an intermittent basis, for as long as necessary. For example, the patient can self-administer a GLP-1 molecule at the first symptom of cardiac distress, and a GLP-1 molecule can thereafter be administered during the time that the patient is in transit to the hospital, and continued during hospitalization, as necessary. Thus, the GLP-1 molecule can be administered at the first cardiac symptom, up until the time a Q-wave MI occurs. In the event that such a QMI occurs following the administration of a GLP-I molecule, the pretreatment of the patient with GLP-1 will ameliorate the tissue damage that results from the MI. In alternative embodiments, the invention includes methods of administering GLP-1 at the first symptom of cardiac distress, and continuing that administration during the time that the individual suffers a QMI. In still further embodiments, the invention includes continuing administration of a GLP-1 molecule after the individual has suffered a QMI. The administration of GLP-1 following a QMI will ameliorate the tissue damage that results from the QMI and subsequent reperfusion-induced injury.

Summary of Invention Paragraph:
[0067] GLP-1 molecules, particularly GLP-1(7-36)amide, act to quickly suppress FFA levels and to optimize aberrant glucose metabolism in the heart, via a variety of mechanisms. In particular, GLP-1(7-36)amide acts to suppress glucagon secretion from pancreatic .alpha.-cells. GLP-1(7-36)amide has no known serious adverse side effects and can be administered at high doses without risking hypoglycemia or hyperglycemia. GLP-1 molecules are ideal for optimizing glucose metabolism in a variety of individuals, including those with impaired glucose tolerance, and those with elevated or aberrant blood glucose levels that are induced by certain conditions, such as stress-related cardiac conditions, and cardiac ischemia induced by UA or NQCN. The present invention contemplates treatment of individuals suffering from one or more of a variety of cardiac system disturbances or disorders, including but not limited to UA and NQCN, which are described in this application. In other embodiments, the inventive early stage treatment of UA can optionally be continued during and after a QMI. In various embodiments of the invention, these therapeutic methods include treatment of individuals with diabetes, including NIDDM, impaired glucose tolerance, and stress hyperglycemia.

Summary of Invention Paragraph:
[0071] Treatment with GLP-1 will ameliorate the adverse effects of cardiac tissue ischemia. First, GLP-1 molecules promote glucose utilization by cardiac tissue, providing valuable energy. GLP-1 thus optimizes tissue utilization and metabolism of glucose, the major energy source during cardiac ischemia. Second, GLP-1-molecule-mediated suppression of glucagon will limit insulin antagonism and reduce circulating FFAs, thus favoring glucose oxidation. These effects of GLP-1 are critical, because glucose oxidation consumes less oxygen than fatty acid oxidation.

Summary of Invention Paragraph:
[0074] It is known in the art that the PTCA procedure itself can result in the release of small emboli, which can, in turn, cause cardiac ischemia when they become lodged in blood vessels.

Accordingly, another embodiment of the invention is the treatment of a patient undergoing PTCA, with a GLP-1 molecule. The GLP-1 molecule will optimize metabolism, and hence ameliorate or prevent the ischemic damage caused by the PTCA-induced release of emboli. In one embodiment, the GLP-1 molecule is administered continuously during the PTCA procedure. In other embodiments, administration of a GLP-1 molecule begins before the PTCA procedure, and continues during the procedure. In yet other embodiments, the GLP-1 molecule administration is continued after the PTCA procedure is completed. In yet other embodiments, the invention includes administering a GLP-1 molecule to a patient undergoing PTCA, wherein the patient has not suffered a Q-wave MI. In other embodiments, the patient has not exhibited a pathological Q-wave.

Summary of Invention Paragraph:
[0080] The use of a GLP-1 molecule in the early stages of ACS, during UA and/or NQCN, will serve to optimize myocardial use of energy substrates, and will limit ischemia-induced damage. Such use of GLP-1 will have the effect of decreasing tissue damage, morbidity and mortality that is associated with UA, NQCN, and Q-wave MI.

Summary of Invention Paragraph:
[0081] The invention also encompasses a method for treatment of an individual with an established diagnosis of ACS (UA or NQCN) in whom there is-as yet-no evidence of an established Q-wave MI, in order to preserve and salvage at-risk myocardial tissue in the ischemic and peri-ischemic zones. Such treatment will comprise the administration of intravenous GLP-1 by continuous infusion, in an appropriate liquid formulation, at a dose of 0.1-10.0 pmol/kg/min, preferably 1.0-3.0 pmol/kg/min, for periods of several hours and up to 10 days, preferably for one to three days. Said continuous intravenous infusion of GLP-1 can be an isolated treatment, or in conjunction with the co-administration of intravenous glucose, as a continuous infusion of a 5-10% solution, and/or the co-administration of potassium, as a continuous infusion of a solution of a suitable potassium salt (such as potassium chloride or potassium acetate) that will supply sufficient potassium to maintain "normal" plasma potassium levels of about 4-5 mM. Typically the solution for administration of potassium will be about 40 mM, but the skilled artisan will recognize that any concentration of potassium can be used, so long as it supplies the desired dosage to the patient. Suitable rates for administration of potassium are between about 40 and about 120 .mu.mol/kg/hr. Co-infusion with glucose is known to enhance and maintain the insulinotropic drive of GLP-1; co-infusion of potassium is known to correct the hypokalemia that can potentially result from intracellular potassium shifts that accompany insulin-mediated glucose uptake.

Detail Description Paragraph:
[0090] Animal models may be used to test the efficacy of the administration of GLP-1 to an individual with unstable angina, but without yet having suffered an actual infarction. Rat models and dog models have been found to be particularly well suited for this purpose. In rats, GLP-1 administered during the last 10 min. of a 25 min. ischemia period and then throughout a 2-hour reperfusion period significantly reduced infarct size (30%), and the rats also had significantly improved hemodynamics. In dogs, administration of GLP-1 significantly reduced the stunning period, during reperfusion after a period of subcritical ischemia.

Detail Description Paragraph:
[0092] GLP-1 (1.5 .mu.g/kg/min) was infused into anesthetized rats (n=10), commencing 10 minutes prior to reperfusion and continuing throughout the 2-hour reperfusion. Controls were sham operated with no occlusion (n=7), LAD occlusion+reperfusion+administration of saline (n=12), and LAD occlusion and reperfusion with a buffer of 10 mM sodium acetate, 5.05% D-mannitol, pH 4.5, ("vehicle") at 1.5 mL/kg/hour (n=10).

Detail Description Paragraph:
[0095] When compared with the vehicle group, infusion of GLP-1 caused a statistically significant ($p<0.05$) reduction in infarct size of approximately 33%. Thus, the systemic administration of GLP-1 can reduce myocardial infarct size even when administered after occlusion of a coronary artery and prior to onset of reperfusion.

Detail Description Paragraph:

[0096] Two dogs were studied at baseline before, during, and for 6 hours after a 10-minute complete left circumflex coronary (LCx) occlusion. Each dog underwent occlusion/reperfusion in the presence and absence of GLP-1 infusion for 24 hours, beginning 1 minute prior to reperfusion. GLP-1 infusion enhanced the recovery of ventricular wall regional dysfunction following 10 minutes of coronary artery occlusion. The study shows that the recovery after ischemia and the reduced stunning in the presence of GLP-1 are not due to increased coronary flow compared to controls, but presumably reflect favorable changes in myocardial energetics.

CLAIMS:

44. A method for treatment of a patient with ischemic heart disease, or is at risk for developing ischemic heart disease, and who exhibits one or more of the following symptoms: nausea, shortness of breath, palpitations and dizziness, and further wherein said patient does not exhibit chest pain, comprising administering to the patient a therapeutically effective amount of a GLP-1 molecule, wherein said patient is not suffering from a Q-wave myocardial infarction.

☐ 2. Document ID: US 20020147131 A1

L3: Entry 2 of 6 File: PGPB Oct 10, 2002

DOCUMENT-IDENTIFIER: US 20020147131 A1

TITLE: Metabolic intervention with GLP-1 to improve the function of ischemic and reperfused skeletal muscle tissue

Abstract Paragraph:
Individuals in need of treatment of ischemia-related reperfusion are treated, preferably intravenously, with a composition which includes a compound which binds to a receptor for the glucagon-like peptide-1. The invention relates to both the method and compositions for such treatment.

Summary of Invention Paragraph:
[0002] This invention relates to metabolic intervention with GLP-1 to therapeutically improve the function of ischemic and reperfused tissue.

Summary of Invention Paragraph:
[0016] Individuals in need of treatment of ischemia and/or reperfusion are treated, preferably intravenously, with a composition which includes a compound which binds to a receptor for the glucagon-like peptide-1. The invention relates to both the method and compositions for such treatment.

Detail Description Paragraph:
[0017] GLP-1 is a glucose-dependent insulinotropic hormone that effectively enhances peripheral glucose uptake without inducing dangerous hypoglycemia. Further, GLP-1 strongly suppresses glucagon secretion, independent of its insuliniotropic action, and thereby powerfully reduces plasma free fatty acid (FFA) levels substantially more than can be accomplished with insulin. High FFA levels have been implicated as a major toxic mechanism during myocardial ischemia.

Detail Description Paragraph:
[0018] We have now developed the concept of GLP-1 as a metabolic therapy for ischemia-reperfusion injury. This development was based on the realization that there are two clinical

situations in which ischemia-reperfusion is a routine, and potentially dangerous, event: thrombolytic procedures for acute MI, and cardiac reperfusion following ischemic cardioplegia during heart surgery. Moreover, recent experimental and clinical data have established that the phenomenon of ischemia-reperfusion is particularly responsive to metabolic therapy with GIK infusion, even more so than isolated ischemia without reperfusion (Apstein, CS (1998) Glucose-insulin-potassium for acute myocardial infarction. Remarkable results from a new prospective, randomized trial. Circulation 98, 2223-2226).

Detail Description Paragraph:
[0019] The two most important therapeutic advances in the treatment of acute ischemia coincident with MI in the past decade have been the introduction of thrombolysis and .beta.-blockade. However, despite this overall success, some studies of thrombolysis have revealed an early excess mortality, which has been attributed to reperfusion-induced injury and myocardial stunning. The mechanisms underlying stunning are complex, but an emerging consensus is that this is likely related to intracellular acidosis leading to dysfunctional sarcolemmal Ca.sup.2+ pumps and cytosolic Ca.sup.2+ overload. The net result is impaired myocardial contractile function leading to decreased mechanical efficiency, as well as reperfusion ventricular arrhythmias. Moreover, recent research has established that the intracellular acidosis, in turn, is due to an imbalance between glycolysis and complete glucose oxidation, in the sense that the rate of glycolysis is uncoupled from the oxidation of pyruvate (the end product of glycolysis) in the TCA cycle. This uncoupling results in net H.sup.+ production due to conversion of pyruvate to lactate. The most likely cause for this imbalance is the presence of high plasma free fatty acid (FFA) levels, which preferentially enter the mitochondria and inhibit pyruvate oxidation, a mechanism that elegantly accounts for the well established observation that hearts perfused with FFA are less able to recover in the reperfusion phase than hearts perfused with glucose. It has here been discovered, and is one of the bases of this therapeutic invention that GLP-1 suppresses FFA beyond what is expected with insulin which is at the 50% level of suppression, and GLP-1 can be as high as 90% suppression of FFA.

Detail Description Paragraph:
[0026] The dual capacity of GLP-1 to powerfully stimulate insulin release and inhibit glucagon secretion, together with the strict glucose-dependence of its insulinotropic action, endow this molecule with a unique therapeutic potential in the management of ischemia-reperfusion. First, GLP-1 strongly stimulates the secretion of endogenous insulin and therefore can be used to achieve all of the beneficial actions attributed to an insulin infusion in the metabolic treatment of ischemia-reperfusion. Although high-dose GIK infusions typically contain 25-33% glucose and 50-100 U insulin/L, the requirement for introduction of hyperglycemia per se to achieve therapeutic efficacy, versus only providing a metabolic milieu for the safe administration of high doses of insulin, is unclear. It is likely that adequate blood glucose levels are required to enable substrate delivery, but this does not necessarily imply a need for hyperglycemia and should not detract from the fact that insulin exerts important effects other than glucose uptake. Therefore, a therapeutic GLP-1 infusion will likely only require a modest (e.g., 5%) glucose coinfusion in order to maintain blood glucose at slightly above physiological levels in order to trigger insulin release. Glucose is not required as a safety measure, since blood levels of .ltoreq.3.5 mM abrogate the insulin-stimulating activity of GLP-1, thereby completely protecting against the dangers of hypoglycemia.

Detail Description Paragraph:
[0027] Second, GLP-1 exerts a powerful glucagonostatic effect, which together with its insulinotropic action will lead to a strong suppression of FFAs. One of the major benefits of glucose-insulin infusions is the reduction in circulating FFA levels and the suppression of FFA uptake. FFAs and their metabolites have direct toxic effects on the ischemic myocardium as well as during the reperfusion period, when they contribute to stunning, and hence reduction of FFA levels is a major therapeutic goal of metabolic intervention in ischemia-reperfusion, goal of metabolic intervention in ischemia-reperfusion. As glucagon is a powerful stimulus for adipose tissue lipolysis and FFA production, GLP-1 mediated glucagon suppression further augments the insulin-induced reduction in circulating FFAs. Thus, GLP-1 therapy is superior to a glucose-insulin infusion in this regard. Indeed, preliminary data in healthy volunteers indicate that an intravenous GLP-1 infusion will reduce fasting plasma FFA levels to <10% of control values.

Detail Description Paragraph:
[0029] In addition to GLP-1 or its biological analogues, the therapy can include use of free radical scavengers such as glutathione, melatonin, Vitamin E, and superoxide dismutase (SOD). In such combinations reperfusion damage risk is lessened even further.

Detail Description Paragraph:
[0044] Patients administered GLP-1 or its analogues in combination with the carrier systems here enumerated, especially those treated before a planned event or within the first 4 hours after an ischemic event, are observed to have less arrhythmia, less tissue damage, and less discomfort without side effects.

Detail Description Paragraph:
[0045] From these considerations it is evident that an infusion of GLP-1 can be expected to exert a major therapeutic effect in myocardial reperfusion. It is expected that GLP-1 can be administered either by I.V. or subcutaneous administration for continuous infusion by intravenous (I.V.)0.1 pmol/kg/min to 10 pmol/kg/min and by subcutaneous (S.C.) 0.1 pmol/kg/min to 75 pmol/kg/min, and for single injection (bolus) by I.V. 0.005 nmol/kg to 20 nmol/kg and S.C. 0.1 nmol/kg to 100 nmol/kg are suitable levels of administration. The GLP-1 infusion can be coadministered with glucose (5%) if required to maintain blood glucose levels .gtoreq.5 mM (to maintain efficient insulin secretion). Similarly, coadministration of potassium (K.sup.+) will also be considered, depending on the extent to which activation of the membrane Na.sup.+/K.sup.+ ATPase leads to a shift of K.sup.+ into the intracellular space. The GLP-1 treatment will be commenced as early in the post-ischemic period as possible after, for example, acute spontaneous ischemia in the home or ambulance context and before reperfusion therapies, and continued thereafter. In the case of cardiac surgery, the GLP-1 infusion should commence 12-24 hours prior to surgery, during surgery from the onset of anesthesia until aortic crossclamping, and immediately after unclamping for a period of at least 72 hours postoperatively. As earlier explained, co-administration of a free radical scavenger will further aid reperfusion recovery.

CLAIMS:

1. A method for amelioration of organ tissue injury caused by reperfusion of blood flow following a period of ischemia, which comprises: administering to an individual in need of such treatment an effective amount of a composition which includes a compound which binds to a receptor for glucagon-like peptide-1, in a pharmaceutical carrier.

14. The method of metabolic intervention with GLP-1 to improve the function of ischemic and reperfused tissue, said method comprising: administering to an individual in need of such treatment an effective amount of a composition comprising GLP-1 in a pharmaceutical carrier.

23. A composition for use in metabolic intervention with GLP-1 to improve the function of ischemic and reperfused tissue, comprising: an effective amount of GLP-1 in combination with a pharmaceutically effective carrier.

☐ 3. Document ID: US 20020107206 A1

L3: Entry 3 of 6 File: PGPB Aug 8, 2002

DOCUMENT-IDENTIFIER: US 20020107206 A1
TITLE: Treatment of acute coronary syndrome with GLP-1

Abstract Paragraph:

The invention relates to methods for treating a patient suffering from acute coronary syndrome, but who is not suffering from a Q-wave myocardial infarction, comprising administration of a therapeutically effective amount of a GLP-1 molecule. The GLP-1 can be self-administered, and can be administered in one or more doses, as needed, on an intermittent or continuous basis, to optimize metabolism in cardiac tissue and to prevent cardiac damage associated with ischemia.

Summary of Invention Paragraph:
[0012] (2) A method for treatment of a patient, comprising administering to the individual a therapeutically effective amount of a GLP-1 molecule, wherein the administration is after the onset of one or more of the following symptoms: chest pain lasting longer than 15 minutes, chest pain at rest, chest pain following minimal exertion, nausea, shortness of breath, palpitations, or dizziness. The above method, wherein the patient has not suffered a Q-wave MI prior to the onset of the symptom or symptoms. The above method, wherein the patient is suffering from unstable angina. The above method, wherein the patient is suffering from non-Q-wave cardiac necrosis. The above method, wherein the patient has a blood troponin I level of no more than 0.4 ng/ml. The above method, wherein the patient has a blood troponin T level of no more than 0.1 ng/ml. The above method, wherein the patient does not have elevated blood creatine kinase myocardial isoenzyme. The above method, wherein the patient does not have ST-segment elevation. The above method, wherein the patient does not exhibit a pathological Q-wave. The above method, wherein the administration occurs between the time of onset of the one or more symptoms, and the time the patient suffers a Q-wave MI. The above method, further comprising the step of continuing the administration of a GLP-1 molecule during the time that the patient suffers a Q-wave MI. The above method, further comprising the step of continuing the administration of a GLP-1 molecule after the time the patient suffers a Q-wave MI. The above method, wherein the patient has ischemic heart disease, or is at risk for developing ischemic heart disease. The above method, wherein the patient has one or more of the following cardiac abnormalities: congestive heart failure, worsening heart murmur due to mitral regurgitation, or evidence of cardiac conduction disturbances. The above method, wherein the patient has a normal ECG. The above method, wherein the patient has stable angina. The above method, wherein the patient administers the GLP-1 to himself. The above method, wherein the GLP-1 is administered in the form of a GLP-1-stick. The above method, wherein the GLP-1 is administered in a single dose. The above method, wherein the GLP-1 is administered in more than one dose. The above method, wherein the GLP-1 is administered continuously. The above method, wherein glucose, or a potassium salt, or a combination thereof, is co-administered with the GLP-1.

Summary of Invention Paragraph:
[0015] (5) A method for treatment of a patient with ischemic heart disease, or is at risk for developing ischemic heart disease, and who exhibits one or more of the following symptoms: nausea, shortness of breath, palpitations, or dizziness, and further wherein the patient does not exhibit chest pain, comprising administering to the patient a therapeutically effective amount of a GLP-1 molecule, wherein the patient is not suffering a Q-wave MI. The above method, wherein the patient has a normal ECG.

Summary of Invention Paragraph:
[0018] Thus, the invention encompasses novel methods for the treatment of acute coronary syndrome, particularly unstable angina and non-Q-wave cardiac necrosis, with a GLP-1 molecule. The methods of the present invention can be used beginning at the earliest stages of ACS, prior to development of a Q-wave MI, to prevent damage associated with ischemia that occurs during Q-wave MI. The inventive therapeutic methods that use a GLP-1 molecule reverse or ameliorate the ischemia-induced damage that occurs during UA and NQCN. The methods of the invention further comprise continuing the treatment with a GLP-1 molecule during or after the time that a patient suffers from a QMI.

Summary of Invention Paragraph:
[0054] The timing and dosage of a GLP-1 molecule, according to the methods of the invention, will depend on the nature of the condition being treated. As discussed here, a GLP-1 molecule may be administered as soon as there is a symptom of cardiac distress, and the administration can be continued, either continuously or or an intermittent basis, for as long as necessary. For example, the patient can self-administer a GLP-1 molecule at the first symptom of cardiac

distress, and a GLP-1 molecule can thereafter be administered during the time that the patient is in transit to the hospital, and continued during hospitalization, as necessary. Thus, the GLP-1 molecule can be administered at the first cardiac symptom, up until the time a Q-wave MI occurs. In the event that such a QMI occurs following the administration of a GLP-1 molecule, the pretreatment of the patient with GLP-1 will ameliorate the tissue damage that results from the MI. In alternative embodiments, the invention includes methods of administering GLP-1 at the first symptom of cardiac distress, and continuing that administration during the time that the individual suffers a QMI. In still further embodiments, the invention includes continuing administration of a GLP-1 molecule after the individual has suffered a QMI. The administration of GLP-1 following a QMI will ameliorate the tissue damage that results from the QMI and subsequent reperfusion-induced injury.

Summary of Invention Paragraph:
[0058] GLP-1 molecules, particularly GLP-1(7-36)amide, act to quickly suppress FFA levels and to optimize aberrant glucose metabolism in the heart, via a variety of mechanisms. In particular, GLP-1(7-36)amide acts to suppress glucagon secretion from pancreatic .alpha.-cells. GLP-1(7-36)amide has no known serious adverse side effects and can be administered at high doses without risking hypoglycemia or hyperglycemia. GLP-1 molecules are ideal for optimizing glucose metabolism in a variety of individuals, including those with impaired glucose tolerance, and those with elevated or aberrant blood glucose levels that are induced by certain conditions, such as stress-related cardiac conditions, and cardiac ischemia induced by UA or NQCN. The present invention contemplates treatment of individuals suffering from one or more of a variety of cardiac system disturbances or disorders, including but not limited to UA and NQCN, which are described in this application. In other embodiments, the inventive early stage treatment of UA can optionally be continued during and after a QMI. In various embodiments of the invention, these therapeutic methods include treatment of individuals with diabetes, including NIDDM, impaired glucose tolerance, and stress hyperglycemia.

Summary of Invention Paragraph:
[0062] Treatment with GLP-1 will ameliorate the adverse effects of cardiac tissue ischemia. First, GLP-1 molecules promote glucose utilization by cardiac tissue, providing valuable energy. GLP-1 thus optimizes tissue utilization and metabolism of glucose, the major energy source during cardiac ischemia. Second, GLP-1-molecule-mediated suppression of glucagon will limit insulin antagonism and reduce circulating FFAs, thus favoring glucose oxidation. These effects of GLP-1 are critical, because glucose oxidation consumes less oxygen than fatty acid oxidation.

Summary of Invention Paragraph:
[0065] It is known in the art that the PTCA procedure itself can result in the release of small emboli, which can, in turn, cause cardiac ischemia when they become lodged in blood vessels. Accordingly, another embodiment of the invention is the treatment of a patient undergoing PTCA, with a GLP-1 molecule. The GLP-1 molecule will optimize metabolism, and hence ameliorate or prevent the ischemic damage caused by the PTCA-induced release of emboli. In one embodiment, the GLP-1 molecule is administered continuously during the PTCA procedure. In other embodiments, administration of a GLP-1 molecule begins before the PTCA procedure, and continues during the procedure. I yet other embodiments, the GLP-1 molecule administration is continued after the PTCA procedure is completed. In yet other embodiments, the invention includes administering a GLP-1 molecule to a patient undergoing PTCA, wherein the patient has not suffered a Q-wave MI. In other embodiments, the patient has not exhibited a pathological Q-wave.

Summary of Invention Paragraph:
[0070] The use of a GLP-1 molecule in the early stages of ACS, during UA and/or NQCN, will serve to optimize myocardial use of energy substrates, and will limit ischemia-induced damage. Such use of GLP-1 will have the effect of decreasing tissue damage, morbidity and mortality that is associated with UA, NQCN, and Q-wave MI.

Summary of Invention Paragraph:
[0071] The invention also encompasses a method for treatment of an individual with an established diagnosis of ACS (UA or NQCN) in whom there is--as yet--no evidence of an

established Q-wave MI, in order to preserve and salvage at-risk myocardial tissue in the ischemic and peri-ischemic zones. Such treatment will comprise the administration of intravenous GLP-1 by continuous infusion, in an appropriate liquid formulation, at a dose of 0.1-10.0 pmol/kg/min, preferably 1.0-3.0 pmol/kg/min, for periods of several hours and up to 10 days, preferably for one to three days. Said continuous intravenous infusion of GLP-1 can be an isolated treatment, or in conjunction with the co-administration of intravenous glucose, as a continuous infusion of a 5-10% solution, and/or the co-administration of potassium, as a continuous infusion of a solution of a suitable potassium salt (such as potassium chloride or potassium acetate) that will supply sufficient potassium to maintain "normal" plasma potassium levels of about 4-5 mM. Typically the solution for administration of potassium will be about 40 mM, but the skilled artisan will recognize that any concentration of potassium can be used, so long as it supplies the desired dosage to the patient. Suitable rates for administration of potassium are between about 40 and about 120 .mu.mol/kg/hr. Co-infusion with glucose is known to enhance and maintain the insulinotropic drive of GLP-1; co-infusion of potassium is known to correct the hypokalemia that can potentially result from intracellular potassium shifts that accompany insulin-mediated glucose uptake.

Detail Description Paragraph:
[0080] Animal models may be used to test the efficacy of the administration of GLP-1 to an individual with unstable angina, but without yet having suffered an actual infarction. Rat models and dog models have been found to be particularly well suited for this purpose. In rats, GLP-1 administered during the last 10 min. of a 25 min. ischemia period and then throughout a 2-hour reperfusion period significantly reduced infarct size (30%), and the rats also had significantly improved hemodynamics. In dogs, administration of GLP-1 significantly reduced the stunning period, during reperfusion after a period of subcritical ischemia.

Detail Description Paragraph:
[0082] GLP-1 (1.5 .mu.g/kg/min) was infused into anesthetized rats (n=10), commencing 10 minutes prior to reperfusion and continuing throughout the 2-hour reperfusion. Controls were sham operated with no occlusion (n=7), LAD occlusion +reperfusion +administration of saline (n=12), and LAD occlusion and reperfusion with a buffer of 10 mM sodium acetate, 5.05% D-mannitol, pH 4.5, ("vehicle") at 1.5 mL/kg/hour (n=10).

Detail Description Paragraph:
[0085] When compared with the vehicle group, infusion of GLP-1 caused a statistically significant ($p<0.05$) reduction in infarct size of approximately 33%. Thus, the systemic administration of (GLP-1 can reduce myocardial infarct size even when administered after occlusion of a coronary artery and prior to onset of reperfusion.

Detail Description Paragraph:
[0086] Two dogs were studied at baseline before, during, and for 6 hours after a 10-minute complete left circumflex coronary (LCx) occlusion. Each dog underwent occlusion/reperfusion in the presence and absence of GLP-1 infusion for 24 hours, beginning 1 minute prior to reperfusion. GLP-1 infusion enhanced the recovery of ventricular wall regional dysfunction following 10 minutes of coronary artery occlusion. The study shows that the recovery after ischemia and the reduced stunning in the presence of GLP-1 are not due to increased coronary flow compared to controls, but presumably reflect favorable changes in myocardial energetics.

CLAIMS:

44. A method for treatment of a patient with ischemic heart disease, or is at risk for developing ischemic heart disease, and who exhibits one or more of the following symptoms: nausea, shortness of breath, palpitations and dizziness, and further wherein said patient does not exhibit chest pain, comprising administering to the patient a therapeutically effective amount of a GLP-1 molecule, wherein said patient is not suffering from a Q-wave myocardial infarction.

☐ 4. Document ID: US 20020055460 A1

L3: Entry 4 of 6 File: PGPB May 9, 2002

DOCUMENT-IDENTIFIER: US 20020055460 A1
TITLE: Metabolic intervention with GLP-1 to improve the function of ischemic and reperfused tissue

Abstract Paragraph:
Individuals in need of treatment of ischemia-related reperfusion are treated, preferably intravenously, with a composition which includes a compound which binds to a receptor for the glucagon-like peptide-1. The invention relates to both the method and compositions for such treatment.

Summary of Invention Paragraph:
[0002] This invention relates to metabolic intervention with GLP-1 to therapeutically improve the function of ischemic and reperfused tissue.

Summary of Invention Paragraph:
[0016] Individuals in need of treatment of ischemia and/or reperfusion are treated, preferably intravenously, with a composition which includes a compound which binds to a receptor for the glucagon-like peptide-1. The invention relates to both the method and compositions for such treatment.

Detail Description Paragraph:
[0017] GLP-1 is a glucose-dependent insulinotropic hormone that effectively enhances peripheral glucose uptake without inducing dangerous hypoglycemia. Further, GLP-1 strongly suppresses glucagon secretion, independent of its insuliniotropic action, and thereby powerfully reduces plasma free fatty acid (FFA) levels substantially more than can be accomplished with insulin. High FFA levels have been implicated as a major toxic mechanism during myocardial ischemia.

Detail Description Paragraph:
[0018] We have now developed the concept of GLP-1 as a metabolic therapy for ischemia-reperfusion injury. This development was based on the realization that there are two clinical situations in which ischemia-reperfusion is a routine, and potentially dangerous, event: thrombolytic procedures for acute MI, and cardiac reperfusion following ischemic cardioplegia during heart surgery. Moreover, recent experimental and clinical data have established that the phenomenon of ischemia-reperfusion is particularly responsive to metabolic therapy with GIK infusion, even more so than isolated ischemia without reperfusion (Apstein, CS (1998) Glucose-insulin-potassium for acute myocardial infarction. Remarkable results from a new prospective, randomized trial. Circulation 98, 2223-2226).

Detail Description Paragraph:
[0019] The two most important therapeutic advances in the treatment of acute ischemia coincident with MI in the past decade have been the introduction of thrombolysis and .beta.-blockade. However, despite this overall success, some studies of thrombolysis have revealed an early excess mortality, which has been attributed to reperfusion-induced injury and myocardial stunning. The mechanisms underlying stunning are complex, but an emerging consensus is that this is likely related to intracellular acidosis leading to dysfunctional sarcolemmal Ca.sup.2+ pumps and cytosolic Ca.sup.2+ overload. The net result is impaired myocardial contractile function leading to decreased mechanical efficiency, as well as reperfusion ventricular arrhythmias. Moreover, recent research has established that the intracellular acidosis, in turn, is due to an imbalance between glycolysis and complete glucose oxidation, in the sense that the rate of glycolysis is uncoupled from the oxidation of pyruvate (the end product of

glycolysis) in the TCA cycle. This uncoupling results in net H.sup.+ production due to conversion of pyruvate to lactate. The most likely cause for this imbalance is the presence of high plasma free fatty acid (FFA) levels, which preferentially enter the mitochondria and inhibit pyruvate oxidation, a mechanism that elegantly accounts for the well-established observation that hearts perfused with FFA are less able to recover in the reperfusion phase than hearts perfused with glucose. It has here been discovered, and is one of the bases of this therapeutic invention that GLP-1 suppresses FFA beyond what is expected with insulin which is at the 50% level of suppression, and GLP-1 can be as high as 90% suppression of FFA.

Detail Description Paragraph:
[0026] The dual capacity of GLP-1 to powerfully stimulate insulin release and inhibit glucagon secretion, together with -the strict glucose-dependence of its insulinotropic action, endow this molecule with a unique therapeutic potential in the management of ischemia-reperfusion. First, GLP-1 strongly stimulates the secretion of endogenous insulin and therefore can be used to achieve all of the beneficial actions attributed to an insulin infusion in the metabolic treatment of ischemia-reperfusion. Although high-dose GIK infusions typically contain 25-33% glucose and 50-100 U insulin/L, the requirement for introduction of hyperglycemia per se to achieve therapeutic efficacy, versus only providing a metabolic milieu for the safe administration of high doses of insulin, is unclear. It is likely that adequate blood glucose levels are required to enable substrate delivery, but this does not necessarily imply a need for hyperglycemia and should not detract from the fact that insulin exerts important effects other than glucose uptake. Therefore, a therapeutic GLP-1 infusion will likely only require a modest (e.g., 5%) glucose coinfusion in order to maintain blood glucose at slightly above physiological levels in order to trigger insulin release. Glucose is not required as a safety measure, since blood levels of <3.5 mM abrogate the insulin-stimulating activity of GLP-1, thereby completely protecting against the dangers of hypoglycemia.

Detail Description Paragraph:
[0027] Second, GLP-1 exerts a powerful glucagonostatic effect, which together with its insulinotropic action will lead to a strong suppression of FFAs. One of the major benefits of glucose-insulin infusions is the reduction in circulating FFA levels and the suppression of FFA uptake. FFAs and their metabolites have direct toxic effects on the ischemic myocardium as well as during the reperfusion period, when they contribute to stunning, and hence reduction of FFA levels is a major therapeutic goal of metabolic intervention in ischemia-reperfusion, goal of metabolic intervention in ischemia-reperfusion. As glucagon is a powerful stimulus for adipose tissue lipolysis and FFA production, GLP-1 mediated glucagon suppression further augments the insulin-induced reduction in circulating FFAs. Thus, GLP-1 therapy is superior to a glucose-insulin infusion in this regard. Indeed, preliminary data in healthy volunteers indicate that an intravenous GLP-1 infusion will reduce fasting plasma FFA levels to <10% of control values.

Detail Description Paragraph:
[0029] In addition to GLP-1 or its biological analogues, the therapy can include use of free radical scavengers such as glutathione, melatonin, Vitamin E, and superoxide dismutase (SOD). In such combinations reperfusion damage risk is lessened even further.

Detail Description Paragraph:
[0044] Patients administered GLP-1 or its analogues in combination with the carrier systems here enumerated, especially those treated before a planned event or within the first 4 hours after an ischemic event, are observed to have less arrhythmia, less tissue damage, and less discomfort without side effects.

Detail Description Paragraph:
[0045] From these considerations it is evident that an infusion of GLP-1 can be expected to exert a major therapeutic effect in myocardial reperfusion. It is expected that GLP-1 can be administered either by I.V. or subcutaneous administration for continuous infusion by intravenous (I.V.)0.1 pmol/kg/min to 10 pmol/kg/min and by subcutaneous (S.C.) 0.1 pmol/kg/min to 75 pmol/kg/min, and for single injection (bolus) by I.V. 0.005 nmol/kg to 20 nmol/kg and S.C. 0.1 nmol/kg to 100 nmol/kg are suitable levels of administration. The GLP-1 infusion can be coadministered with glucose (5%) if required to maintain blood glucose levels .gtoreq.5 mM (to maintain efficient insulin secretion). Similarly, coadministration of potassium (K.sup.+)

will also be considered, depending on the extent to which activation of the membrane Na.sup.+/K.sup.+ ATPase leads to a shift of K.sup.+ into the intracellular space. The GLP-1 treatment will be commenced as early in the post-ischemic period as possible after, for example, acute spontaneous ischemia in the home or ambulance context and before reperfusion therapies, and continued thereafter. In the case of cardiac surgery, the GLP-1 infusion should commence 12-24 hours prior to surgery, during surgery from the onset of anesthesia until aortic crossclamping, and immediately after unclamping for a period of at least 72 hours postoperatively. As earlier explained, co-administration of a free radical scavenger will further aid reperfusion recovery.

CLAIMS:

1. A method for amelioration of organ tissue injury caused by reperfusion of blood flow following a period of ischemia, which comprises: administering to an individual in need of such treatment an effective amount of a composition which includes a compound which binds to a receptor for glucagon-like peptide-1, in a pharmaceutical carrier.

14. The method of metabolic intervention with GLP-1 to improve the function of ischemic and reperfused tissue, said method comprising: administering to an individual in need of such treatment an effective amount of a composition comprising GLP-1 in a pharmaceutical carrier.

23. A composition for use in metabolic intervention with GLP-1 to improve the function of ischemic and reperfused tissue, comprising: an effective amount of GLP-1 in combination with a pharmaceutically effective carrier.

☐ 5. Document ID: US 6706689 B2

L3: Entry 5 of 6 File: USPT Mar 16, 2004

DOCUMENT-IDENTIFIER: US 6706689 B2
TITLE: Treatment of acute coronary syndrome with GLP-1

Abstract Text (1):
The invention relates to methods for treating a patient suffering from acute coronary syndrome, but who is not suffering from a Q-wave myocardial infarction, comprising administration of a therapeutically effective amount of a GLP-1 molecule. The GLP-1 can be self-administered, and can be administered in one or more doses, as needed, on an intermittent or continuous basis, to optimize metabolism in cardiac tissue and to prevent cardiac damage associated with ischemia.

Brief Summary Text (12):
Objects of the present invention include the following: (1) A method of treating a patient suffering from acute coronary syndrome, comprising administering to the patient a therapeutically effective amount of a GLP-1 molecule, wherein the patient is not suffering from a Q-wave MI. The above method, wherein the patient is suffering from unstable angina. The above method, wherein the patient is suffering from non-Q-wave cardiac necrosis. The above method, wherein the patient has a blood troponin I level of no more than 0.4 ng/ml. The above method, wherein the patient has a blood troponin T level of no more than 0.1 ng/ml. The above method, wherein the patient does not have elevated blood creatine kinase. The above method, wherein the patient does not have ST-segment elevation. The above method, wherein the patient does not exhibit a pathological Q-wave. The above method, wherein the patient exhibits one or more of the following symptoms: chest pain greater than 15 minutes in duration, chest pain at rest, or chest pain following minimal exertion that is poorly responsive to sublingual nitrates. The above method, wherein the patient has stable angina. The above method, wherein the patient

administers the GLP-1 to himself. The above method, wherein the GLP-1 is administered in the form of a GLP-1-stick. The above method, wherein the GLP-1 is administered in a single dose. The above method, wherein the GLP-1 is administered in more than one dose. The above method, wherein the GLP-1 is administered continuously. The above method, wherein glucose, or a potassium salt, or a combination thereof, is co-administered with the GLP-1. (2) A method for treatment of a patient, comprising administering to the individual a therapeutically effective amount of a GLP-1 molecule, wherein the administration is after the onset of one or more of the following symptoms: chest pain lasting longer than 15 minutes, chest pain at rest, chest pain following minimal exertion, nausea, shortness of breath, palpitations, or dizziness. The above method, wherein the patient has not suffered a Q-wave MI prior to the onset of the symptom or symptoms. The above method, wherein the patient is suffering from unstable angina. The above method, wherein the patient is suffering from non-Q-wave cardiac necrosis. The above method, wherein the patient has a blood troponin I level of no more than 0.4 ng/ml. The above method, wherein the patient has a blood troponin T level of no more than 0.1 ng/ml. The above method, wherein the patient does not have elevated blood creatine kinase myocardial isoenzyme. The above method, wherein the patient does not have ST-segment elevation. The above method, wherein the patient does not exhibit a pathological Q-wave. The above method, wherein the administration occurs between the time of onset of the one or more symptoms, and the time the patient suffers a Q-wave MI. The above method, further comprising the step of continuing the administration of a GLP-1 molecule during the time that the patient suffers a Q-wave MI. The above method, further comprising the step of continuing the administration of a GLP-1 molecule after the time the patient suffers a Q-wave MI. The above method, wherein the patient has ischemic heart disease, or is at risk for developing ischemic heart disease. The above method, wherein the patient has one or more of the following cardiac abnormalities: congestive heart failure, worsening heart murmur due to mitral regurgitation, or evidence of cardiac conduction disturbances. The above method, wherein the patient has a normal ECG. The above method, wherein the patient has stable angina. The above method, wherein the patient administers the GLP-1 to himself. The above method, wherein the GLP-1 is administered in the form of a GLP-1-stick. The above method, wherein the GLP-1 is administered in a single dose. The above method, wherein the GLP-1 is administered in more than one dose. The above method, wherein the GLP-1 is administered continuously. The above method, wherein glucose, or a potassium salt, or a combination thereof, is co-administered with the GLP-1. (3) A method for treating a patient suffering from stable angina, comprising administration of a GLP-1 molecule. The above method, wherein the administration is continuous. (4) A method for performing angioplasty on a patient in need thereof, comprising administering a GLP-1 molecule to the patient during the angioplasty procedure. The above method, further comprising administering a GLP-1 molecule to the patient prior to the angioplasty procedure. The above method, further comprising administering a GLP-1 molecule to the patient following the angioplasty procedure. (5) A method for treatment of a patient with ischemic heart disease, or is at risk for developing ischemic heart disease, and who exhibits one or more of the following symptoms: nausea, shortness of breath, palpitations, or dizziness, and further wherein the patient does not exhibit chest pain, comprising administering to the patient a therapeutically effective amount of a GLP-1 molecule, wherein the patient is not suffering a Q-wave MI. The above method, wherein the patient has a normal ECG. (6) A method for increasing the time during which thrombolytic therapy will be effective following the first symptom of cardiac distress, comprising administering a therapeutically effective amount of a GLP-1 molecule after the onset of one or more of the following symptoms: chest pain lasting longer than 15 minutes, chest pain at rest, chest pain following minimal exertion, nausea, shortness of breath, palpitations, or dizziness. (7) A kit comprising one or more doses of a GLP-1 molecule, the kit comprising a device selected from the group consisting of an insulin-type syringe, a "pen" injector that delivers a metered dose, a needle-less injector, a liquid-formulation, a dry-powder inhaler, a buccal tablet, and a sublingual tablet.

Brief Summary Text (14):
Thus, the invention encompasses novel methods for the treatment of acute coronary syndrome, particularly unstable angina and non-Q-wave cardiac necrosis, with a GLP-1 molecule. The methods of the present invention can be used beginning at the earliest stages of ACS, prior to development of a Q-wave MI, to prevent damage associated with ischemia that occurs during Q-wave MI. The inventive therapeutic methods that use a GLP-1 molecule reverse or ameliorate the ischemia-induced damage that occurs during UA and NQCN. The methods of the invention further

comprise continuing the treatment with a GLP-1 molecule during or after the time that a patient suffers from a QMI.

Brief Summary Text (50):
The timing and dosage of a GLP-1 molecule, according to the methods of the invention, will depend on the nature of the condition being treated. As discussed here, a GLP-1 molecule may be administered as soon as there is a symptom of cardiac distress, and the administration can be continued, either continuously or or an intermittent basis, for as long as necessary. For example, the patient can self-administer a GLP-1 molecule at the first symptom of cardiac distress, and a GLP-1 molecule can thereafter be administered during the time that the patient is in transit to the hospital, and continued during hospitalization, as necessary. Thus, the GLP-1 molecule can be administered at the first cardiac symptom, up until the time a Q-wave MI occurs. In the event that such a QMI occurs following the administration of a GLP-1 molecule, the pretreatment of the patient with GLP-1 will ameliorate the tissue damage that results from the MI. In alternative embodiments, the invention includes methods of administering GLP-1 at the first symptom of cardiac distress, and continuing that administration during the time that the individual suffers a QMI. In still further embodiments, the invention includes continuing administration of a GLP-1 molecule after the individual has suffered a QMI. The administration of GLP-1 following a QMI will ameliorate the tissue damage that results from the QMI and subsequent reperfusion-induced injury.

Brief Summary Text (54):
GLP-1 molecules, particularly GLP-1(7-36)amide, act to quickly suppress FFA levels and to optimize aberrant glucose metabolism in the heart, via a variety of mechanisms. In particular, GLP-1(7-36)amide acts to suppress glucagon secretion from pancreatic .alpha.-cells. GLP-1(7-36) amide has no known serious adverse side effects and can be administered at high doses without risking hypoglycemia or hyperglycemia. GLP-1 molecules are ideal for optimizing glucose metabolism in a variety of individuals, including those with impaired glucose tolerance, and those with elevated or aberrant blood glucose levels that are induced by certain conditions, such as stress-related cardiac conditions, and cardiac ischemia induced by UA or NQCN. The present invention contemplates treatment of individuals suffering from one or more of a variety of cardiac system disturbances or disorders, including but not limited to UA and NQCN, which are described in this application. In other embodiments, the inventive early stage treatment of UA can optionally be continued during and after a QMI. In various embodiments of the invention, these therapeutic methods include treatment of individuals with diabetes, including NIDDM, impaired glucose tolerance, and stress hyperglycemia.

Brief Summary Text (58):
Treatment with GLP-1 will ameliorate the adverse effects of cardiac tissue ischemia. First, GLP-1 molecules promote glucose utilization by cardiac tissue, providing valuable energy. GLP-1 thus optimizes tissue utilization and metabolism of glucose, the major energy source during cardiac ischemia. Second, GLP-1-molecule-mediated suppression of glucagon will limit insulin antagonism and reduce circulating FFAs, thus favoring glucose oxidation. These effects of GLP-1 are critical, because glucose oxidation consumes less oxygen than fatty acid oxidation.

Brief Summary Text (61):
It is known in the art that the PTCA procedure itself can result in the release of small emboli, which can, in turn, cause cardiac ischemia when they become lodged in blood vessels. Accordingly, another embodiment of the invention is the treatment of a patient undergoing PTCA, with a GLP-1 molecule. The GLP-1 molecule will optimize metabolism, and hence ameliorate or prevent the ischemic damage caused by the PTCA-induced release of emboli. In one embodiment, the GLP-1 molecule is administered continuously during the PTCA procedure. In other embodiments, administration of a GLP-1 molecule begins before the PTCA procedure, and continues during the procedure. I yet other embodiments, the GLP-1 molecule administration is continued after the PTCA procedure is completed. In yet other embodiments, the invention includes administering a GLP-1 molecule to a patient undergoing PTCA, wherein the patient has not suffered a Q-wave MI. In other embodiments, the patient has not exhibited a pathological Q-wave.

Brief Summary Text (66):

The use of a GLP-1 molecule in the early stages of ACS, during UA and/or NQCN, will serve to optimize myocardial use of energy substrates, and will limit ischemia-induced damage. Such use of GLP-1 will have the effect of decreasing tissue damage, morbidity and mortality that is associated with UA, NQCN, and Q-wave MI.

Brief Summary Text (67):
The invention also encompasses a method for treatment of an individual with an established diagnosis of ACS (UA or NQCN) in whom there is--as yet--no evidence of an established Q-wave MI, in order to preserve and salvage at-risk myocardial tissue in the ischemic and peri-ischemic zones. Such treatment will comprise the administration of intravenous GLP-1 by continuous infusion, in an appropriate liquid formulation, at a dose of 0.1-10.0 pmol/kg/min, preferably 1.0-3.0 pmol/kg/min, for periods of several hours and up to 10 days, preferably for one to three days. Said continuous intravenous infusion of GLP-1 can be an isolated treatment, or in conjunction with the co-administration of intravenous glucose, as a continuous infusion of a 5-10% solution, and/or the co-administration of potassium, as a continuous infusion of a solution of a suitable potassium salt (such as potassium chloride or potassium acetate) that will supply sufficient potassium to maintain "normal" plasma potassium levels of about 4-5 mM. Typically the solution for administration of potassium will be about 40 mM, but the skilled artisan will recognize that any concentration of potassium can be used, so long as it supplies the desired dosage to the patient. Suitable rates for administration of potassium are between about 40 and about 120 .mu.mol/kg/hr. Co-infusion with glucose is known to enhance and maintain the insulinotropic drive of GLP-1; co-infusion of potassium is known to correct the hypokalemia that can potentially result from intracellular potassium shifts that accompany insulin-mediated glucose uptake.

Detailed Description Text (2):
Animal models may be used to test the efficacy of the administration of GLP-1 to an individual with unstable angina, but without yet having suffered an actual infarction. Rat models and dog models have been found to be particularly well suited for this purpose. In rats, GLP-1 administered during the last 10 min. of a 25 min. ischemia period and then throughout a 2-hour reperfusion period significantly reduced infarct size (30%), and the rats also had significantly improved hemodynamics. In dogs, administration of GLP-1 significantly reduced the stunning period, during reperfusion after a period of subcritical ischemia.

Detailed Description Text (5):
GLP-1 (1.5 .mu.g/kg/min) was infused into anesthetized rats (n=10), commencing 10 minutes prior to reperfusion and continuing throughout the 2-hour reperfusion. Controls were sham operated with no occlusion (n=7), LAD occlusion+reperfusion+administration of saline (n=12), and LAD occlusion and reperfusion with a buffer of 10 mM sodium acetate, 5.05% D-mannitol, pH 4.5, ("vehicle") at 1.5 mL/kg/hour (n=10).

Detailed Description Text (8):
When compared with the vehicle group, infusion of GLP-1 caused a statistically significant ($p<0.05$) reduction in infarct size of approximately 33%. Thus, the systemic administration of (GLP-1 can reduce myocardial infarct size even when administered after occlusion of a coronary artery and prior to onset of reperfusion.

Detailed Description Text (10):
Two dogs were studied at baseline before, during, and for 6 hours after a 10-minute complete left circumflex coronary (LCx) occlusion. Each dog underwent occlusion/reperfusion in the presence and absence of GLP-1 infusion for 24 hours, beginning 1 minute prior to reperfusion. GLP-1 infusion enhanced the recovery of ventricular wall regional dysfunction following 10 minutes of coronary artery occlusion. The study shows that the recovery after ischemia and the reduced stunning in the presence of GLP-1 are not due to increased coronary flow compared to controls, but presumably reflect favorable changes in myocardial energetics.

CLAIMS:

17. A method for treatment of a patient suffering from one or more conditions selected from the group consisting of unstable angina, non-Q-wave cardiac necrosis, ischemic heart disease, and

stable angina, comprising administering to said individual a therapeutically effective amount of a GLP-1 molecule, wherein said administration is after the onset of one or more of the following symptoms: chest pain lasting longer than 15 minutes, chest pain at rest, chest pain following minimal exertion, nausea, shortness of breath, palpitations, or dizziness.

39. A method for treatment of a patient with ischemic heart disease, or at risk for developing ischemic heart disease, and who exhibits one or more of the following symptoms: nausea, shortness of breath, palpitations and dizziness, and further wherein said patient does not exhibit chest pain, comprising administering to the patient a therapeutically effective amount of a GLP-1 molecule, wherein said patient is not suffering from a myocardial infarction.

☐ 6. Document ID: US 6284725 B1

L3: Entry 6 of 6 File: USPT Sep 4, 2001

DOCUMENT-IDENTIFIER: US 6284725 B1
TITLE: Metabolic intervention with GLP-1 to improve the function of ischemic and reperfused tissue

Abstract Text (1):
Individuals in need of treatment of ischemia-related reperfusion are treated, preferably intravenously, with a composition which includes a compound which binds to a receptor for the glucagon-like peptide-1. The invention relates to both the method and compositions for such treatment.

Brief Summary Text (2):
This invention relates to metabolic intervention with GLP-1 to therapeutically improve the function of ischemic and reperfused tissue.

Detailed Description Text (3):
Individuals in need of treatment of ischemia and/or reperfusion are treated, preferably intravenously, with a composition which includes a compound which binds to a receptor for the glucagon-like peptide-1. The invention relates to both the method and compositions for such treatment.

Detailed Description Text (5):
GLP-1 is a glucose-dependent insulinotropic hormone that effectively enhances peripheral glucose uptake without inducing dangerous hypoglycemia. Further, GLP-1 strongly suppresses glucagon secretion, independent of its insuliniotropic action, and thereby powerfully reduces plasma free fatty acid (FFA) levels substantially more than can be accomplished with insulin. High FFA levels have been implicated as a major toxic mechanism during myocardial ischemia.

Detailed Description Text (6):
We have now developed the concept of GLP-1 as a metabolic therapy for ischemia-reperfusion injury. This development was based on the realization that there are two clinical situations in which ischemia-reperfusion is a routine, and potentially dangerous, event: thrombolytic procedures for acute MI, and cardiac reperfusion following ischemic cardioplegia during heart surgery. Moreover, recent experimental and clinical data have established that the phenomenon of ischemia-reperfusion is particularly responsive to metabolic therapy with GIK infusion, even more so than isolated ischemia without reperfusion (Apstein, CS (1998) Glucose-insulin-potassium for acute myocardial infarction. Remarkable results from a new prospective,

randomized trial. Circulation 98, 2223-2226).

Detailed Description Text (7):
The two most important therapeutic advances in the treatment of acute ischemia coincident with MI in the past decade have been the introduction of thrombolysis and .beta.-blockade. However, despite this overall success, some studies of thrombolysis have revealed an early excess mortality, which has been attributed to reperfusion-induced injury and myocardial stunning. The mechanisms underlying stunning are complex, but an emerging consensus is that this is likely related to intracellular acidosis leading to dysfunctional sarcolemmal Ca.sup.2+ pumps and cytosolic Ca.sup.2+ overload. The net result is impaired myocardial contractile function leading to decreased mechanical efficiency, as well as reperfusion ventricular arrhythmias. Moreover, recent research has established that the intracellular acidosis, in turn, is due to an imbalance between glycolysis and complete glucose oxidation, in the sense that the rate of glycolysis is uncoupled from the oxidation of pyruvate (the end product of glycolysis) in the TCA cycle. This uncoupling results in net H.sup.+ production due to conversion of pyruvate to lactate. The most likely cause for this imbalance is the presence of high plasma free fatty acid (FFA) levels, which preferentially enter the mitochondria and inhibit pyruvate oxidation, a mechanism that elegantly accounts for the well-established observation that hearts perfused with FFA are less able to recover in the reperfusion phase than hearts perfused with glucose. It has here been discovered, and is one of the bases of this therapeutic invention that GLP-1 suppresses FFA beyond what is expected with insulin which is at the 50% level of suppression, and GLP-1 can be as high as 90% suppression of FFA.

Detailed Description Text (14):
The dual capacity of GLP-1 to powerfully stimulate insulin release and inhibit glucagon secretion, together with the strict glucose-dependence of its insulinotropic action, endow this molecule with a unique therapeutic potential in the management of ischemia-reperfusion. First, GLP-1 strongly stimulates the secretion of endogenous insulin and therefore can be used to achieve all of the beneficial actions attributed to an insulin infusion in the metabolic treatment of ischemia-reperfusion. Although high-dose GIK infusions typically contain 25-33% glucose and 50-100 U insulin/L, the requirement for introduction of hyperglycemia per se to achieve therapeutic efficacy, versus only providing a metabolic milieu for the safe administration of high doses of insulin, is unclear. It is likely that adequate blood glucose levels are required to enable substrate delivery, but this does not necessarily imply a need for hyperglycemia and should not detract from the fact that insulin exerts important effects other than glucose uptake. Therefore, a therapeutic GLP-1 infusion will likely only require a modest (e.g., 5%) glucose coinfusion in order to maintain blood glucose at slightly above physiological levels in order to trigger insulin release. Glucose is not required as a safety measure, since blood levels of .ltoreq.3.5 mM abrogate the insulin-stimulating activity of GLP-1, thereby completely protecting against the dangers of hypoglycemia.

Detailed Description Text (15):
Second, GLP-1 exerts a powerful glucagonostatic effect, which together with its insulinotropic action will lead to a strong suppression of FFAs. One of the major benefits of glucose-insulin infusions is the reduction in circulating FFA levels and the suppression of FFA uptake. FFAs and their metabolites have direct toxic effects on the ischemic myocardium as well as during the reperfusion period, when they contribute to stunning, and hence reduction of FFA levels is a major therapeutic goal of metabolic intervention in ischemia-reperfusion, goal of metabolic intervention in ischemia-reperfusion. As glucagon is a powerful stimulus for adipose tissue lipolysis and FFA production, GLP-1 mediated glucagon suppression further augments the insulin-induced reduction in circulating FFAs. Thus, GLP-1 therapy is superior to a glucose-insulin infusion in this regard. Indeed, preliminary data in healthy volunteers indicate that an intravenous GLP-1 infusion will reduce fasting plasma FFA levels to <10% of control values.

Detailed Description Text (17):
In addition to GLP-1 or its biological analogues, the therapy can include use of free radical scavengers such as glutathione, melatonin, Vitamin E, and superoxide dismutase (SOD). In such combinations reperfusion damage risk is lessened even further.

Detailed Description Text (32):

Patients administered GLP-1 or its analogues in combination with the carrier systems here enumerated, especially those treated before a planned event or within the first 4 hours after an ischemic event, are observed to have less arrhythmia, less tissue damage, and less discomfort without side effects.

Detailed Description Text (33):
From these considerations it is evident that an infusion of GLP-1 can be expected to exert a major therapeutic effect in myocardial reperfusion. It is expected that GLP-1 can be administered either by I.V. or subcutaneous administration for continuous infusion by intravenous (I.V.)0.1 pmol/kg/min to 10 pmol/kg/min and by subcutaneous (S.C.) 0.1 pmol/kg/min to 75 pmol/kg/min, and for single injection (bolus) by I.V. 0.005 nmol/kg to 20 nmol/kg and S.C. 0.1 nmol/kg to 100 nmol/kg are suitable levels of administration. The GLP-1 infusion can be coadministered with glucose (5%) if required to maintain blood glucose levels.gtoreq.5 mM (to maintain efficient insulin secretion). Similarly, coadministration of potassium (K.sup.+) will also be considered, depending on the extent to which activation of the membrane Na.sup.+ /K.sup.+ ATPase leads to a shift of K.sup.+ into the intracellular space. The GLP-1 treatment will be commenced as early in the post-ischemic period as possible after, for example, acute spontaneous ischemia in the home or ambulance context and before reperfusion therapies, and continued thereafter. In the case of cardiac surgery, the GLP-1 infusion should commence 12-24 hours prior to surgery, during surgery from the onset of anesthesia until aortic crossclamping, and immediately after unclamping for a period of at least 72 hours postoperatively. As earlier explained, co-administration of a free radical scavenger will further aid reperfusion recovery.

Term	Documents
GLP-1	1236
GLP-1S	6
GLUCAGON	6652
GLUCAGONS	175
LIKE	2524416
LIKES	6271
PEPTIDE	110570
PEPTIDES	92604
"1"	4290596
1S	16875
TISSUE	261078
((GLP-1 | GLUCAGON LIKE PEPTIDE 1 OR EXENDIN$2) SAME (ISCHEMI$3 AND REPERFUS$4 AND ((TISSUE|ORGAN) ADJ (DAMAGE|DEATH)))).PGPB,USPT.	6

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